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Insulin resistance impairs response to doxazosin therapy in men with benign prostatic hyperplasia

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Aim: To evaluate the effects of insulin resistance (IR) on outcomes of doxazosin treatment for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

Materials and methods: This prospective study included 64 patients with LUTS due to BPH. LUTS were evaluated using the international prostate symptom score (IPSS) and maximum flow rate (Qmax) in uroflowmetry. Diagnosis of IR was achieved using homeostasis model assessment (HOMA) score and patients were grouped with respect to absence (group 1, n = 44) or presence (group 2, n = 20) of IR. Patients were evaluated before and after 3 months of daily doxazosin therapy (4 mg extended release tablet).

Results: Doxazosin significantly improved the IPSS and Qmax in group 1 (P = 0.04 and P = 0.008, respectively). In group 2, doxazosin treatment had no significant therapeutic effect on mean IPSS and Qmax (P = 0.116 and P = 0.477, respectively). On the other hand, doxazosin significantly improved mean HOMA scores of patients with IR (P = 0.015).

Conclusion: IR impairs response to doxazosin treatment for LUTS due to BPH. The presence of IR should be kept in mind in patients refractory to doxazosin therapy.

Key words: Insulin resistance, benign prostatic hyperplasia, doxazosin

1. Introduction

Benign prostatic hyperplasia (BPH) remains one of the most frequent and important health problems of advanced-aged males, which most commonly presents with lower urinary tract symptoms (LUTS) (1). LUTS due to BPH decrease the quality of life as they have a negative impact on daily life and cause bother (2). Alpha-adrenergic receptor blockers and 5-alpha-reductase inhibitors are 2 commonly used groups of medication in the treatment of BPH. The main mechanism of action of alpha-blockers in BPH therapy includes the treatment of symptoms related with BPH's dynamic component by causing relaxation of the smooth muscles in the prostate and bladder neck (3,4).

BPH is histopathologically characterized by the increase in number of epithelial and stromal cells in the periurethral zone of the prostate (5). Some etiological factors, especially some steroidal hormones, were thought to be associated with the pathogenesis of BPH (6,7). However, the exact pathophysiological mechanism(s) that initiate and stimulate the progression of the process are yet to be defined, and the search for new possible etiological factors for BPH is continuously going on. Recently obesity, insulin resistance (IR), dyslipidemia, and hyperinsulinemia were reported to be risk factors associated with BPH (8,9).

Insulin resistance is defined as the deteriorated response to secreted or administered exogenous insulin (10). Recent evidence supports a possible link between BPH and metabolic syndrome, which may or may not be accompanied by IR (11). Insulin resistance is one of the causes of hyperinsulinemia, which is thought to be a key factor in metabolic syndrome–BPH interaction (12). Doxazosin, a selective inhibitor of alpha-1 adrenergic receptors, was demonstrated to have a corrective effect on IR (13).

Effects of IR on the outcomes of doxazosin treatment for LUTS due to BPH were evaluated in this study.

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2. Materials and methods

Between January and July of 2010, 64 patients who applied to our outpatient urology clinic with LUTS due to BPH were included in this study. Patients with diabetes mellitus, neurological disease, prostate cancer, and history of lower urinary tract surgery and patients receiving medical treatment for BPH or using any hormonal medication were excluded from the study. An informed consent was obtained from each patient.

A detailed medical history of every patient was recorded. LUTS were graded with the international prostate symptom score (IPSS). Prostatic examinations were performed by digital rectal exam. Blood tests including serum glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), insulin, and prostate specific antigen (PSA) were performed. Blood samples were collected from the patients after they fasted for 1 night. The serum PSA levels were determined by using the monoclonal Tandem-R kit (Hybritech Inc., San Diego, CA, USA). A PSA level above 4 ng/mL was accepted as an indication for prostate biopsy. Transrectal ultrasound was performed in order to evaluate prostatic morphology and calculate prostate volume. Maximal urinary flow rate (Qmax) in uroflowmetry was recorded.

Fasting serum insulin levels were measured using the radioimmunoassay method (MP Biomedical and Diagnostics, San Diego, CA, USA). Diagnosis of IR was achieved according to the homeostasis model assessment (HOMA) score, which was calculated using the following formula: fasting serum glucose (mmol/L) × fasting serum insulin (μU/mL) / 22.5. A HOMA score of ≥2.5 indicated the presence of IR (14). Patients were grouped with respect to the absence or presence of IR (group 1, n = 44 and group 2, n = 20, respectively). Patients were given doxazosin as 4 mg extended release tablets (Cardura XL 4 mg, Pfizer, NY, USA) daily for at least 3 months and were reevaluated afterwards. Treatment outcome measures were changes in IPSS and Qmax in each group. Posttreatment serum glucose, insulin, and HOMA scores were also recorded.

The results were given as mean ± standard deviation. The 2 groups were compared using the Mann–Whitney U test and comparisons within the groups were made using the Wilcoxon test. P values lower than 0.05 were accepted to be significant.

3. Results

The mean age of the patients was 59.3 ± 6.9 years, IPSS was 11.2 ± 6.4, Qmax was 16.7 ± 9.3 mL/s, and prostate volume was 34.3 ± 19.6 mL. Mean PSA, insulin, glucose, total cholesterol, triglyceride, LDL-C, and HDL-C levels were 2.1 ± 1.9 ng/mL, 10.3 ± 11.0 IU/mL, 88.7 ± 14.8 mg/dL (4.9 ± 0.8 mmol/L), 190.8 ± 46.8 mg/dL, 153.2 ± 121.5 mg/dL, 127.7 ± 40.8 mg/dL, and 38.6 ± 8.7 mg/dL, respectively.

There was no statistically significant difference between the 2 groups regarding mean age, IPSS, Qmax, prostate volume, PSA, total cholesterol, triglyceride, LDL-C, and HDL-C (Table 1). The mean serum insulin level, glucose level, and HOMA score in group 1 were significantly lower than those of the patients in group 2 (5.4 ± 2.5 vs. 21.1 ± 14.5 μIU/mL, 85.1 ± 12.5 vs. 96.7 ± 16.6 mg/dL, and 1.13 ± 0.55 vs. 4.8 ± 3.2, respectively).

Table 1. The clinical and laboratory data of BPH patients in both groups.

	Group 1 (without IR) (n = 44)	Group 2 (with IR) (n = 20)	P
Age (years)	59.8 ± 6.6	58.2 ± 7.7	0.357
IPSS	11.6 ± 6.4	10.4 ± 6.4	0.368
Maximal urine flow rate (mL/s)	16.1 ± 9.3	18.0 ± 9.4	0.396
Prostate volume (mL)	32.1 ± 15.2	39.2 ± 26.8	0.524
Glucose (mg/dL)	85.1 ± 12.5	96.7 ± 16.6	<0.001
HDL-C (mg/dL)	39.4 ± 8.8	36.8 ± 8.4	0.182
LDL-C (mg/dL)	124.8 ± 30.8	134.1 ± 57.7	0.822
Total cholesterol (mg/dL)	188.5 ± 45.9	195.9 ± 49.7	0.772
Triglyceride (mg/dL)	147.9 ± 134.1	164.8 ± 89.8	0.210
PSA (ng/mL)	2.2 ± 2.1	2.0 ± 1.2	0.622
Insulin (μIU/mL)	5.4 ± 2.5	21.1 ± 14.5	<0.001
HOMA score	1.13 ± 0.55	4.8 ± 3.2	<0.001

The posttreatment mean IPSS in group 1 was significantly lower than the pretreatment value (9.0 ± 8.4 vs. 11.6 ± 6.4, P = 0.04), while the respective Qmax and glucose levels were higher than their pretreatment values (17.8 ± 9.1 vs. 16.1 ± 9.3 mL/s and 91.8 ± 20.8 vs. 85.1 ± 12.5 mg/dL) (Table 2). There were no significant differences between pre- and posttreatment values of total cholesterol, triglyceride, LDL-C, and HDL-C in group 1 (Table 2).

Doxazosin treatment did not affect the mean IPSS, Qmax, serum glucose, total cholesterol, LDL-C, and HDL-C levels in group 2 (Table 3). However, the HOMA score significantly improved after doxazosin therapy in group 2 (P = 0.015), while no significant improvement was observed in group 1 (P = 0.916). In group 2, IR was treated with doxazosin therapy in 8 of the patients. The pre- and posttreatment IPSS and Qmax levels were similar in patients without (n = 8) and with (n = 12) IR (9.1 ± 5.0 vs. 6.0 ± 3.9, P = 0.1 and 17.9 ± 11.8 mL/s vs. 16.9 ± 9.9 mL/s, P = 0.5; 11.1 ± 7.3 vs. 8.5 ± 8.2, P = 0.3 and 18.1 ± 8.1 mL/s vs. 20.0 ± 9.1 mL/s, P = 0.1).

Table 2. Clinical and laboratory data before and after doxazosin therapy in BPH patients without insulin resistance (group 1) (n = 44).

	Pretreatment	Posttreatment	P
IPSS	11.6 ± 6.4	9.0 ± 8.4	0.040
Maximal urine flow rate (mL/s)	16.1 ± 9.3	17.8 ± 9.1	0.008
Glucose (mg/dL)	85.1 ± 12.5	91.8 ± 20.8	0.025
HDL-C (mg/dL)	39.4 ± 8.8	43.0 ± 28.7	0.883
LDL-C (mg/dL)	124.8 ± 30.8	124.5 ± 34.1	0.783
Total cholesterol (mg/dL)	188.5 ± 45.9	190.4 ± 38.2	0.117
Triglyceride (mg/dL)	147.9 ± 134.1	143.6 ± 80.2	0.722
Insulin (μIU/mL)	5.4 ± 2.5	6.1 ± 4.9	0.506
HOMA score	1.13 ± 0.55	1.50 ± 1.62	0.916

Table 3. Clinical and laboratory data before and after doxazosin therapy in BPH patients with insulin resistance (group 2) (n = 20).

	Pretreatment	Posttreatment	P
IPSS	10.4 ± 6.4	7.5 ± 6.8	0.116
Maximal urine flow rate (mL/s)	18.0 ± 9.4	18.8 ± 9.3	0.477
Glucose (mg/dL)	96.7 ± 16.6	99.0 ± 15.8	0.585
HDL-C (mg/dL)	36.8 ± 8.4	36.0 ± 7.9	0.265
LDL-C (mg/dL)	134.1 ± 57.7	132.2 ± 36.7	0.968
Total cholesterol (mg/dL)	195.9 ± 49.7	186.7 ± 62.3	0.344
Triglyceride (mg/dL)	164.8 ± 89.8	157.7 ± 76.4	0.778
Insulin (μIU/mL)	21.1 ± 14.5	11.7 ± 6.6	0.005
HOMA score	4.79 ± 3.21	2.96 ± 1.84	0.015

4. Discussion

The components of metabolic syndrome, which is characterized with IR and hyperinsulinemia, are type 2 diabetes mellitus, hypertension, obesity, and dyslipidemia (15–18). These factors have also been reported as risk factors for the development of BPH (19,20). Insulin resistance, together with its consequence, hyperinsulinemia, constitutes an important etiological connection between metabolic syndrome and increased BPH risk (11). Increased serum insulin was shown to be associated with an increased annual growth of total and transitional zone volume of the prostate (11,21). Diabetic patients were not included in our study in an effort to prevent the influence of the effects of diabetes on BPH. This is because diabetes affects bladder functions in ways similar to BPH; diabetic cystopathy causes voiding symptoms and diabetes-induced detrusor instability causes storage symptoms (22,23).

High serum insulin induces prostatic growth via several mechanisms. Hyperinsulinemia has a stimulating effect on the sympathetic nervous system. Insulin facilitates glucose intake in the ventromedial hypothalamic neurons, which regulate the sympathetic system (24). Prostatic obstruction is not only a consequence of static obstruction caused by the prostatic mass, but also a result of the dynamic obstruction caused by the contraction of alpha-adrenergic smooth muscle located in bladder neck and capsule of the prostate (25). The increased sympathetic tone triggered by hyperinsulinemia is also associated with BPH pathophysiology (26). One possible mechanism for the increased BPH risk in hyperinsulinemia is related to the insulin-like growth factor (IGF), which stimulates the growth in prostatic stromal and epithelial cells (27). It was demonstrated that the systemic administration of IGF increases prostatic growth (28). Growth hormone is a major regulator of IGF-1 and IGF-binding protein-3 (29). Insulin regulates the bioactivity of IGF-1. The effect of insulin on IGF-1 is to decrease the synthesis and plasma level of this protein (30). Another proposed mechanism is that the prostatic inflammation observed in metabolic syndrome patients may play an important role in the development and progression of BPH (31).

Doxazosin is one of the most commonly used alpha-blockers for the treatment of BPH. Its clinical efficacy, especially in terms of significant improvements in Qmax and symptom score, is well supported with large studies with adequate duration and number of patients (32). In our study, however, the significant improvements in IPSS and Qmax were only observed in patients without IR, while no significant changes in IPSS and Qmax were observed after doxazosin therapy in patients with IR. When we checked the lipid profile of our patients after doxazosin therapy, we did not detect any significant change. However, there are reports pointing out an improvement in the lipid profile after the therapy (13,33). A challenge for the urologist during BPH treatment is the inability to predict the response of the patient to the applied medication. Although it was shown in a study that the response to alpha-blockers is associated with the area density of prostatic smooth muscle, obviously it has no clinical implication in daily practice (34).

It is known that doxazosin increases insulin sensitivity and decreases serum insulin level (13,35). Similarly, increased physical activity, discontinuation of smoking, decreased intake of saturated fat, intake of food with low glycemic index and high-fiber content, and the use of medications like metformin or captopril are known to increase sensitivity to insulin (11,36). However, to our best knowledge, there are no data regarding the effects of the improvement in IR on BPH symptoms. In our study, no significant improvements in IPSS and Qmax were achieved by doxazosin in BPH patients with IR (n = 20). IR improved in 40% of patients (n = 8) after therapy. However, the similar pre- and posttreatment values of IPSS and Qmax in patients with improved and nonimproved IR suggested that the disappearance of IR after doxazosin had had no impact on the outcomes of BPH therapy. This result may be related to our patients' high baseline HOMA-R scores, shorter duration of treatment, and differences in patient profile.

In conclusion, a respectable ratio of the patients do not respond to medical therapy for BPH with alpha-blockers. The exact reason, and all possible factors related to this failure, are yet to be defined. IR exerts a neutralizing effect on the efficacy of doxazosin therapy for the treatment of LUTS due to BPH. This may be because of the increased sympathetic tonus triggered by hyperinsulinemia, which usually accompanies IR. IR should be kept in mind in the evaluation of patients with LUTS who are refractory to alpha-blocker therapy. The findings of our study should be confirmed with studies on a larger series and using other alpha-blockers.

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